



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 519/00, 501/46, A61K 31/545	A1	(11) International Publication Number: WO 94/29321 (43) International Publication Date: 22 December 1994 (22.12.94)
(21) International Application Number: PCT/KR94/00061 (22) International Filing Date: 2 June 1994 (02.06.94) (30) Priority Data: 1993/10188 5 June 1993 (05.06.93) KR (71) Applicant: CHEIL FOODS & CHEMICALS INC. [KR/KR]; 150, Taepyungro 2-ga, Chung-ku, Seoul 100-102 (KR). (72) Inventors: KIM, Choong, Sup; Changmi Apartment 12-306, Shincheon-dong, Songpa-ku, Seoul 138-240 (KR). AHN, Yang, Soo; Jukong Apartment 912-408, Myungil-dong, Kangdong-ku, Seoul 134-070 (KR). JUNG, Kang, Yeoun; 412-2, Yeokbuk-ri, Yongin-eub, Yongin-kun, Kyonggi-do 449-800 (KR). YUN, Rok, Lim; Hanshin Apartment 105- 310, Inkye-dong, Paldal-ku, Suwon-shi, Kyonggi-do 442- 070 (KR). PARK, Seong, Yong; 370-20, Yeonnam-dong, Mapo-ku, Seoul 121-240 (KR). YOON, Yeo, Hong; 609-10, Kongreung-dong, Nowon-ku, Seoul 139-240 (KR). LEE, Keon, Ho; 502-1601, Eunha Maeul, Choong-dong, Wonmi- ku, Bucheon-shi, Kyonggi-do 421-020 (KR). LYU, Chun, Seon; 614-232, Bangwha 2-dong, Kangseo-ku, Seoul 157- 222 (KR). LEE, Kwang, Ho; Shinsigazi Apartment 405- 1904, Mok-dong, Yangcheon-ku, Seoul 158-050 (KR).	(74) Agent: LEE, Kuiy, Dong; 114-31, Uni-dong, Chongro-ku, Seoul 110-350 (KR). (81) Designated States: CN, JP, RU, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.	
(54) Title: NOVEL CEPHEM COMPOUNDS <div style="text-align: center;"> <p>(I)</p> </div> (57) Abstract <p>The present invention relates to novel cephem compounds having formula (I) wherein Q is a carbon or nitrogen atom; X is an oxygen atom, or a nitroalkylenyl or cyanoimine group, with the proviso that X cannot be an oxygen atom when Q is a carbon atom; R₁ is a hydrogen atom, or a lower alkyl group, or a lower alkyl group which may be substituted by fluoro, or by a carboxylic group or an inorganic cation salt thereof; and R₂ and R₃ independently are a hydrogen atom or a lower alkyl group; or pharmaceutically acceptable salts thereof. The compounds of the present invention have potent antibacterial activities against gram-negative bacteria, especially <i>Pseudomonas</i>, and a longer half-life than conventional cephem compounds.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

NOVEL CEPHEM COMPOUNDS

TECHNICAL FIELD

5 The present invention relates to novel cephem compounds and pharmaceutically acceptable salts thereof having potent antibacterial activities against gram-negative bacteria and an extended duration of action.

BACKGROUND ART

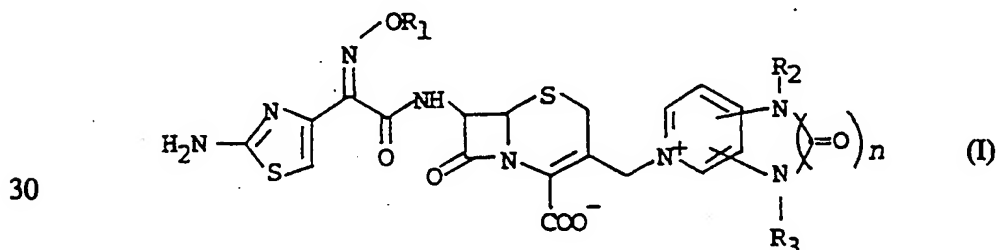
10

Since the first synthesis of cephem compounds in which the cephem nucleus has a carboxylic group at 4-position and a substituted amino group at 7-position, an extensive investigation has been made to develop a novel structure of cephem derivatives having more potent antibacterial activities and a broad antibacterial spectrum.

As prior art references which disclose such derivatives, U.S. Patent No. 4,152,432 to Heymes *et al.*; U.S. Patent No. 4,098,888 to Ochiai *et al.*; U.S. Patent No. 4,258,041 to O'Callaghan; U.S. Patent No. 4,748,172 to Katner; European Patent No. 0,318,552 to Katner; European Patent No. 0,164,944 to Bradbury; and European Patent No. 0,300,664 to Jung may be mentioned.

In most recent years, we have proposed, in our U.S. Serial No. 07/896,667, a class of novel compounds having the formula:

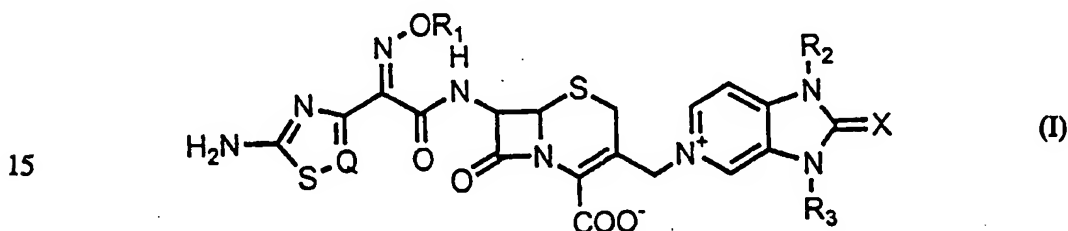
25



DISCLOSURE OF THE INVENTION

We have now found an another class of novel compounds which are neither described nor claimed in U.S. Serial No. 07/896,667. These novel compounds have been proven by the present invention to have potent antibacterial activities against gram-negative bacteria, especially *Pseudomonas*, and a significantly long duration of action.

Thus, in an aspect, the present invention provides novel cephem compounds
10 having the formula:



wherein, Q is a carbon or nitrogen atom; X is an oxygen atom, or a nitroalkyl or cyanoimine group, with the proviso that X cannot be an oxygen atom when Q is a carbon atom; R₁ is a hydrogen atom, a lower alkyl group, or a lower alkyl group which may be substituted by fluoro, or by a carboxylic group or an inorganic cation salt thereof; and R₂ and R₃ independently are a hydrogen atom or a lower alkyl group; or pharmaceutically acceptable salts thereof.

25 As used herein, the term "lower alkyl" refers to alkyl groups having 1 to 5 carbon atoms, such as methyl, ethyl, propyl, isopropyl, *tert*-butyl, butyl, or pentyl, unless otherwise indicated.

Pharmaceutically acceptable salts of the compounds of the formula (I) include an inorganic cation salt, for example, an alkali metal salt (*e.g.*, sodium salt, potassium salt, *etc.*), an alkaline earth metal salt (*e.g.*, calcium salt, magnesium salt, *etc.*); an inorganic acid salt (*e.g.*, hydrochloride, hydrobromide, hydroiodide, sulfate, carbonate, bicarbonate, *etc.*); an organic acid salt (*e.g.*, maleate, lactate, tartarated, *etc.*); a sulfonate (*e.g.*, benzenesulfonate, methanesulfonate, paratoluenesulfonate, *etc.*); a salt with an amino acid such as arginine, lysine, glycine, *etc.*; and an amine

- 3 -

salt (e.g., ammonium salt, trimethylamine salt, triethylamine salt, pyridine salt, procaine salt, picoline salt, etc.), and the like.

Particularly preferred specific compounds according to the invention are as set forth below:

5

7- β -[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-nitromethylen-yl-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

10 7- β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-nitromethylen-yl-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

15 7- β -[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-cyanoimine-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7- β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-cyanoimine-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

20 7- β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7- β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[1-methyl-2(3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

25 7- β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-hydroxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

30 7- β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-carboxymethoxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate; and

7- β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-fluoromethoxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate.

35 The most preferred compounds of the invention are those in which Q is a nitrogen atom; X is an oxygen atom; R₁ is a hydrogen atom, a methyl, fluoromethyl

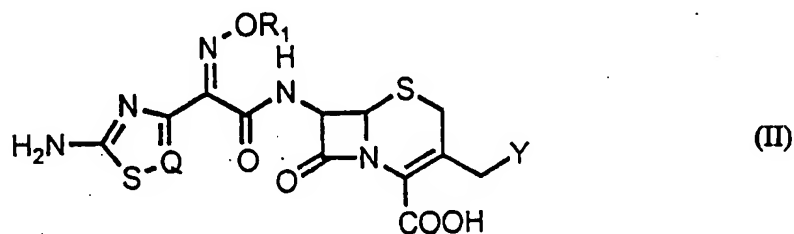
- 4 -

or carboxymethyl group; at least one of R_2 and R_3 is a hydrogen atom.

The compounds according to the present invention have a long duration of action (half-life) and exhibit potent antibacterial activities against gram-negative
5 bacteria such as *Pseudomonas*.

The compounds of the formula (I) and pharmaceutically acceptable salts thereof can be prepared by reacting a compound having the formula (II):

10



15

wherein, Q and R_1 have the same meanings as defined above; and Y is a halogen atom or an acetoxy group;

with a compound having the formula (III):

20

()



25

wherein, X, R_2 and R_3 have the same meanings as defined above.

Preferably, the halogen atom may include chlorine, bromine or iodine, more preferably iodine.

30

According to the invention, a compound of the formula (II) is first silylated with a silylating agent in an aprotic organic solvent to protect the carboxy group at 4-position and the amino group at 7-position, of the cephem nucleus.

35

Such a silylating agent may include N,O-bis(trimethylsilyl)acetamide, N-

- 5 -

methyl-N-(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, N-methyl-N-(trimethyl-silyl)trifluoroacetamide, and hexamethyldisilazane. As an appropriate aprotic organic solvent, there may be mentioned nitriles such as acetonitrile and propionitrile; alkyl halides such as chloroform, carbon tetrachloride
5 and dichloromethane; ethers such as tetrahydrofuran and dioxane; amides such as N,N-dimethylformamide; esters such as ethylacetate and methylacetate; ketones such as acetone, methylethylketone and methylisobutylketone; sulfoxides such as dimethylsulfoxide; and aromatic hydrocarbon solvents such as benzene and toluene.

10 The silylated compound of the formula (II) is then reacted with trimethylsilyliodide (TMSI) at ambient temperature to give a compound of the formula (II) in which Y is iodine. This reaction is disclosed, for example, in U.S. Patent No. 4,266,049 to Bonjouklian and U.S. Patent No. 4,748,172 to Katner.

15 A compound of the formula (III), 2-oxoimidazo pyridine compound, may also be prepared by known methods [See: J. Chem. Soc. (B), 285(1966); J. Org. Chem. 33(6), 2543(1968); J. Org. Chem., 43(3), 393(1978); J. Heterocyclic Chem., 13, 601(1976); J. Heterocyclic Chem., 22, 1061(1985); Syn, Comn., 12(3), 213(1982); Bull. Chem. Soc. Jpn., 60, 1973(1987)], and is silylated with the same silylating
20 agent as mentioned above in an anhydrous aprotic organic solvent.

The silylated 3-iodomethyl cephem compound of the formula (II) is then reacted with a compound of the formula (III) in an anhydrous aprotic solvent to give a silylated compound of the formula (I). Hydrolysis of the silyl group provides a
25 compound of the formula (I) according to the present invention. The resulting compound of the formula (I) is isolated from the reaction mixture and purified by known methods such as extraction using organic solvents, crystallization, column chromatography, and so forth.

30 The compounds of the present invention may be formulated for administration in the form of an injection (e.g., intravenous, intraperitoneal, intramuscular, or subcutaneous injection) in accordance with conventional methods known in the art. Alternatively, the compounds may be formulated into various kinds of dosage forms, for example, capsules, tablets, pills, solutions, suspensions, emulsions, suppositories,
35 pastes, ointments, gels, creams, lotions, powders, and sprays.

- 6 -

Tablets, capsules, pills and granules can contain the active compound or compounds in combination with the customary excipients, such as fillers and extenders, for example, starches, lactose, sucrose, glucose, mannitol and silica; binders, for example, carboxymethyl-cellulose, alginates, gelatine and polyvinyl pyrrolidone; humectants, for example, glycerine; disintegrating agents, for example, agar-agar, calcium carbonate and sodium carbonate; absorption accelerators, for example, quaternary ammonium compounds; wetting agents, for example, cetyl alcohol or glycerine monostearate; adsorbents, for example, kaolin and bentonite; and lubricants, for example, talc, calcium stearate, and magnesium stearate.

10

Suppositories can contain, in addition to the active compound or compounds, customary aqueous or non-aqueous excipients, for example, polyethylene glycols, fats, for example, cacao fat, and higher esters (for example, a C₁₄ alcohol with a C₁₆ fatty acid), or mixtures of these substances.

15

Ointments, pastes, creams and gels can contain customary excipients, in addition to the active compound or compounds, for example, animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silica, talc, and zinc oxide, or mixtures of these substances.

20

() Powders and sprays can also contain customary excipients in addition to the active compound or compounds, for example, lactose, talc, silica, aluminum hydroxide, calcium silicate, and polyamide powders, or mixtures of these substances. Sprays can additionally contain customary propellants, for example, chlorofluorohydrocarbons.

25

Solutions and emulsions can contain customary excipients, in addition to the active compound or compounds, such as solvents, solubilizing agents, and emulsifiers, for example water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, especially cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerine, glycerineformal, tetrahydrofurfuryl alcohol, polyethylene glycols, and fatty acid esters of sorbitan, or mixtures of these substances.

35

- 7 -

For parenteral administration, the solutions and emulsions can also be in sterile form, which is isotonic with blood.

Suspensions can contain customary excipients, in addition to the active compound or compounds, such as liquid diluents, for example, water, ethyl alcohol or propylene glycol, suspending agents, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol esters and sorbitan esters, microcrystalline cellulose, aluminum meta-hydroxide, bentonite, agar-agar, and tragacanth, or mixtures of these substances.

10

BEST MODE FOR CARRING OUT THE INVENTION

The present invention will be described in greater detail by way of the following examples. The examples are presented for illustration purposes only and should not be construed as limiting the invention which is properly delineated in the claims.

Preparation 1: 2-(1H,3H)-Nitromethylen-yl-imidazo[4,5-c]pyridine

1 G of 1,1-bis(methylthio)-2-nitroethylene and 0.6 g of 3,4-diaminopyridine were placed into a 50 ml reaction vessel. To the mixture was added 20 ml of ethyl alcohol. The resulting dispersion was heated to an elevated temperature and stirred under reflux for 10 hrs, while trapping the methanethiol discharged into an aqueous 20 % NaCl solution. Thereafter, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel eluting with dichloroethane:methyl alcohol (2:1) to give 500 mg of the title compound.

IR (KBr, cm^{-1}): 3416; 1517; 1319.

NMR ($\text{DMSO}-d_6$): 7.5(1H, d); 8.2(1H, d); 8.7(1H, s); 7.4(1H, s).

Preparation 2: 2-(1H,3H)-Cyanoimine-imidazo[4,5-c]pyridine

2 G of dimethyl N-cyanodithioiminocarbonate and 1.34 g of 3,4-diaminopyridine were placed into a 100 ml reaction vessel. To the mixture was added 30 ml of acetonitrile. The resulting dispersion was heated to an elevated temperature and stirred under reflux for overnight, while trapping the methanethiol

- 8 -

discharged into an aqueous 20 % NaCl solution. After completion of the reaction, the precipitated solids were filtered out and dissolved in dichloroethane:methyl alcohol (2:1), and then separated by column chromatography on silica gel to give 1 g of the title compound.

5

IR (KBr, cm^{-1}): 2180; 1652; 1604; 1488.

NMR ($\text{DMSO}-d_6$): 7.2(1H, d); 8.2(2H, d); 8.3(1H, s).

Preparation 3: 2-(1H,3H)-Oxo-imidazo[4,5-c]pyridine

10

3 G of 3,4-diaminopyridine and 1.65 g of urea were added to 30 ml of dimethylformamide. The mixture was stirred under reflux for 6 hrs, allowed to cool to room temperature, and stirred further for 12 hrs to precipitate solids. The resulting solids were filtered out, and dissolved in methyl alcohol. The resulting solution was treated with active carbon, and concentrated under reduced pressure to give 3.1 g of the title compound as a white solid.

15

IR (KBr, cm^{-1}): 3125; 1717; 1630.

NMR ($\text{DMSO}-d_6$) : 8.14(1H, s); 8.10(1H, d); 6.97(1H, d).

20

Preparation 4: 1-Methyl-2(3H)-oxo-imidazo[4,5-c]pyridine

4.3 G of 4-methylamino-3-aminopyridine and 2.1 g of urea were added to 43 ml of dimethylformamide. The resulting mixture was stirred under reflux for 4 hrs, and then allowed to cool to room temperature. The resulting solids were filtered out, and dissolved in methyl alcohol under reflux. The solution was then cooled slowly to precipitate solids. The solution containing the precipitated solids were stirred further for 1 hr and filtered out to give 3.9 g of the title compound as a white solid.

25
30

IR (KBr, cm^{-1}): 2739; 1715; 1624.

NMR ($\text{DMSO}-D_2O$): 8.18(1H, s); 8.13(1H, d); 7.1(1H, d); 3.27(3H, s).

Example 1: 7- β -[(Z)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-nitromethylen-yl-imidazo[4,5-c]pyridiniummethyl-3-cephem-4-carboxylate

35

500 Mg of 7- β -[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxy-methyl-3-cephem-4-carboxylic acid was suspended in 10 ml of dry dichloromethane. The resulting suspension was added to 0.7 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide at room temperature. The reaction mixture was stirred for 1 hr to effect silylation. To the silylated solution was added 0.38 ml of iodotrimethylsilane at 0 °C. The reaction mixture was stirred for 30 mins at room temperature. Thereafter, the mixture was concentrated, and then the concentrate was dissolved in a mixture of 10 ml of acetonitrile and 1.0 ml of tetrahydrofuran to produce a solution. Separately, 200 mg of 2-(1H,3H)-nitromethylen-yl-imidazo[4,5-c]pyridine was dissolved in a mixture of 10 ml of acetonitrile and 0.79 ml of N,O-bis(trimethylsilyl)acetamide. The resulting solution was subjected to silylation for 1.5 hrs to give a silylated pyridine derivative. The derivative was added to the solution previously obtained, and the mixture was allowed to react at room temperature for 3 hrs. Then, to the reaction mixture was added a mixed solvent of 0.5 ml of methyl alcohol and 5 ml of acetonitrile to effect deprotection. The reaction mixture was stirred at 0 °C for 30 mins. The resulting solids were filtered out, dissolved in 10 ml of water while adjusting the pH to 6.5 with sodium bicarbonate, and then concentrated. The residue was purified by chromatography on silica gel with acetonitrile:water (4:1) to give 181 mg of the title compound.

IR (KBr, cm^{-1}): 3420; 1760; 1670; 1520; 1320.

NMR ($\text{DMSO}-d_6$): 3.14(1H, d); 3.52(1H, d); 3.76(3H, s); 5.17(1H, d); 5.30(1H, d), 5.71(1H, d), 5.79(1H, d); 6.69(1H, s); 7.11(2H, br), 8.17(1H, d); 8.45(1H, d); 9.01(1H, s), 9.53(1H, d).

Example 2: 7- β -[(Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-nitromethylen-yl-imidazo[4,5-c]-pyridiniummethyl]-3-cephem-4-carboxylate

30

500 Mg of 7- β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was suspended in 10 ml of dry dichloromethane. To the resultant suspension was added 0.8 ml of N-methyl-N-(trimethylsilyl)trifluoroacetamide. The mixture was stirred at room temperature for 1 hr to effect silylation. To the silylated solution was added slowly

35

- 10 -

0.40 ml of iodotrimethylsilane at 0 °C. The reaction mixture was allowed to stand at room temperature, stirred for 30 mins, and then concentrated. The concentrate was dissolved in a mixture of 10 ml of acetonitrile and 1.0 ml of tetrahydrofuran to produce a solution. Separately, 202 mg of 2-(1H,3H)-nitro-methylen-yl-imidazo[4,5-c]pyridine was dissolved in a mixture of 10 ml of acetonitrile and 0.81 ml of N,O-bis(trimethylsilyl)acetamide. The resulting solution was subjected to silylation for 1.5 hrs to give a silylated pyridine derivative, which was then added to the solution previously obtained. The mixture was allowed to react at room temperature for 3 hrs. Then, to the reaction mixture was added a mixed solvent of 0.5 ml of methyl alcohol and 5 ml of acetonitrile to effect deprotection. The reaction mixture was stirred at 0 °C for 30 mins. Then, the resulting solids were filtered out and dissolved in 10 ml of water while adjusting the pH to 6.5 with sodium bicarbonate, and then concentrated. The residue was purified by column chromatography on silica gel with acetonitrile:water (4:1) to give 165 mg of the title compound.

15

IR (KBr, cm^{-1}): 3400; 2200; 1750; 1652; 1604.

NMR ($\text{DMSO}-d_6$): 3.14(1H, d); 3.49(1H, d); 3.78(3H, s); 5.14(1H, d); 5.19(1H, d), 5.70(1H, d); 5.80(1H, m); 7.64(1H, d), 8.0(2H, br); 8.75(1H, d); 9.21(1H, s).

20 Example 3: 7- β -[(Z)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-cyanoimine-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate

The title compound was prepared by reacting 700 mg of 7- β -[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid with 230 mg of 2-(1H,3H)-cyanoimine-imidazo[4,5-c]pyridine by the same procedure as described in Example 1.

Yield: 400 mg.

IR (KBr, cm^{-1}): 3401; 2180; 1749; 1652.

30 NMR ($\text{DMSO}-d_6$): 3.11(1H, d); 3.53(1H, d); 3.81(3H, s); 5.18(1H, d); 5.24(1H, d); 5.77(1H, d); 5.85(1H, m); 6.72(1H, s); 7.20(2H, br); 7.44(1H, d); 8.34(1H, d); 8.57(1H, s); 9.57(1H, d).

35 Example 4: 7- β -[(Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-cyanoimine-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate

- 11 -

The title compound was prepared by reacting 500 mg of 7- β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid with 200 mg of 2-(1H,3H)-cyanoimine-imidazo[4,5-c]pyridine by the same procedure as described in Example 2.

5

Yield: 300 mg.

IR (KBr, cm^{-1}): 2412; 1750; 1653.

NMR ($\text{DMSO}-d_6$): 3.12(1H, d); 3.50(1H, d); 3.90(3H, s); 5.12(1H, d); 5.19(1H, d); 5.68(1H, d); 5.83(1H, m); 7.60(1H, d); 8.30(2H, br); 8.72(1H, d); 9.09(1H, s);

10 9.59(1H, d).

Example 5: 7- β -[(Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate

15

The title compound was prepared by reacting 500 mg of 7- β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid with 160 mg of 2-(1H,3H)-oxo-imidazo[4,5-c]pyridine by the same procedure as described in Example 2.

20 Yield: 300 mg

IR (KBr, cm^{-1}): 3400; 1750; 1690.

NMR ($\text{DMSO}-d_6$): 3.1-3.5(2H, q); 4.0(3H, s); 5.1-5.7(2H, q); 5.8(1H, dd); 7.6(1H, s); 8.2(2H, s); 8.8(1H, d); 9.2(1H, s); 9.6(1H, d).

25

Example 6: 7- β -[(Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[1-methyl-2-(3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate

The title compound was prepared by reacting 500 mg of 7- β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-

30

carboxylic acid with 160 mg of 1-methyl-2-(3H)-oxo-imidazo[4,5-c]pyridine by the same procedure as described in Example 2.

Yield: 300 mg

IR (KBr, cm^{-1}): 3401; 1750; 1660.

35 NMR ($\text{DMSO}-d_6$): 3.10(1H, d); 3.30(1H, d); 3.51(3H, s); 3.61(3H, s); 4.94(1H, d);

- 12 -

5.13(1H, d); 5.49(1H, d); 5.73(1H, m); 7.27(1H, d); 8.02(1H, s); 8.56(1H, d); 8.70(1H, s); 9.62(1H, d).

Example 7: 7-β-[(Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-hydroxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate

The title compound was prepared by reacting 500 mg of 7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-hydroxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid with 190 mg of 2-(1H,3H)-oxo-imidazo[4,5-c]pyridine by the same procedure as described in Example 2.

Yield: 200 mg

IR (KBr, cm⁻¹): 3300; 1764; 1651; 1612.

NMR (DMSO-*d*₆): 3.15(1H, d); 3.59(1H, d); 5.13(1H, d); 5.18(1H, d); 5.70(1H, d); 5.81(1H, d); 7.62(1H, d); 8.78(1H, d); 9.16(1H, d); 9.60(1H, d).

Example 8: 7-β-[(Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-carboxymethoxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate

The title compound was prepared by reacting 300 mg of 7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-carboxymethoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid with 250 mg of 2-(1H,3H)-oxo-imidazo[4,5-c]pyridine by the same procedure as described in Example 2.

Yield: 150 mg.

IR (KBr, cm⁻¹): 3200; 1760; 1654; 1615.

NMR (DMSO-*d*₆): 3.28(1H, d); 3.37(1H, d); 4.50(2H, s); 5.12(1H, d); 5.71(1H, d); 5.85(1H, d); 7.46(1H, d); 8.37(1H, d); 8.70(1H, s); 9.47(1H, d).

Example 9: 7-β-[(Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-fluoromethoxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate

The title compound was prepared by reacting 700 mg of 7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-fluoromethoxyiminoacetamido]-3-cephem-4-carboxylic acid

- 13 -

with 300 mg of 2-(1H,3H)-oxo-imidazo[4,5-c]pyridine by the same procedure as described in Example 2.

Yield: 300 mg.

5 IR (KBr, cm^{-1}): 1761; 1652; 1613.

NMR ($\text{DMSO}-d_6$): 3.18(1H, d); 3.57(1H, d); 4.51(1H, s); 5.02(3H, s); 5.32(1H, d); 5.83(1H, d); 7.47(1H, d); 8.36(1H, d); 8.47(1H, s); 8.52(1H, d).

EXPERIMENT 1: In vitro Antibacterial Activity

10

In order to demonstrate the antibacterial activities of the compounds according to the present invention, minimum inhibitory concentration (MIC, $\mu\text{g/ml}$) for each compound synthesized in the above examples was determined in accordance with the method described in Chemotherapy, 29(1), p. 96 (1981).

15

As reference compounds, Cefotaxime (CTX), Ceftazidime (CAZ) and Cefpirome (CPR) were employed. The results are shown in Table 1 below.

Table 1

Minimum Inhibitory Concentration of the Present Compounds (MIC, $\mu\text{g/ml}$)

5	Compound	Ex. 1	Ex. 2	Ex. 3	Ex. 4
	Strain				
	1. <i>S. pyogenes</i> ATCC 8668	0.007	0.013	0.004	0.007
	2. <i>S. pyogenes</i> C4003	0.007	0.007	0.004	0.007
10	3. <i>S. faecalis</i> ATCC 29212	> 100.000	> 100.000	> 100.000	> 100.000
	4. <i>S. aureus</i> Smith	0.780	3.130	1.560	3.130
	5. <i>S. aureus</i> ATCC 29213	1.560	1.560	3.130	3.130
	6. <i>S. aureus</i> C4036	1.560	3.130	3.130	3.130
	7. MRSA C2208	> 100.000	> 100.000	> 100.000	> 100.000
15	8. <i>S. epidermidis</i> ATCC12228	0.780	1.560	0.780	1.560
	9. <i>E. coli</i> C4002	0.100	0.100	0.050	0.100
	10. <i>E. coli</i> ATCC 10536	0.050	0.050	0.013	0.050
	11. <i>E. coli</i> ATCC 25922	0.100	0.100	0.050	0.100
	12. <i>E. cloacae</i> C4008	0.050	0.050	0.013	0.050
20	13. <i>E. cloacae</i> C4009	0.200	0.200	0.025	0.050
(14. <i>K. oxytoca</i> C4022	6.250	12.500	6.250	12.500
	15. <i>K. pneumoniae</i> C1040	0.025	0.050	0.025	0.025
	16. <i>K. pneumoniae</i> ATCC 10031	0.025	0.050	0.007	0.013
25	17. <i>P. mirabilis</i> ATCC 25933	0.100	0.100	0.025	0.025
	18. <i>P. rettgeri</i> ATCC 9919	0.013	0.025	0.007	0.013
	19. <i>S. typhimurium</i> C4045	0.100	0.200	0.025	0.050
	20. <i>S. marcescens</i> C1052	0.200	0.200	0.050	0.050
30	21. <i>S. marcescens</i> ATCC 27117	0.100	0.200	0.025	0.050
	22. <i>P. aeruginosa</i> C2027	6.250	6.250	6.250	6.250
	23. <i>P. aeruginosa</i> ATCC10145	50.000	50.000	12.500	12.500
	24. <i>P. aeruginosa</i> ATCC27853	50.000	> 100.000	6.250	25.000
	25. <i>P. aeruginosa</i> C4070	> 100.000	> 100.000	12.500	12.500

Table 1 (Continued)

5	Compound	Ex. 5	Ex. 6	Ex. 7	Ex. 8
	Strain				
	1. <i>S. pyogenes</i> ATCC 8668	0.013	0.007	0.100	0.100
	2. <i>S. pyogenes</i> C4003	0.013	0.004	0.200	0.196
	3. <i>S. faecalis</i> ATCC 29212	> 100.000	> 100.000	> 100.000	> 100.000
	4. <i>S. aureus</i> Smith	1.560	3.130	6.250	3.130
10	5. <i>S. aureus</i> ATCC 29213	1.560	3.130	0.780	0.780
	6. <i>S. aureus</i> C4036	1.560	3.130	1.560	1.560
	7. MRSA C2208	> 100.000	> 100.000	> 100.000	> 100.000
	8. <i>S. epidermidis</i> ATCC12228	0.780	1.560	3.130	1.560
	9. <i>E. coli</i> C4002	0.007	0.025	6.250	3.130
15	10. <i>E. coli</i> ATCC 10536	0.004	0.007	0.025	0.013
	11. <i>E. coli</i> ATCC 25922	0.013	0.025	0.050	0.050
	12. <i>E. cloacae</i> C4008	0.002	0.013	0.100	0.013
	13. <i>E. cloacae</i> C4009	0.007	0.013	0.100	0.013
	14. <i>K. oxytoca</i> C4022	0.780	1.560	1.560	0.782
20	15. <i>K. pneumoniae</i> C1040	0.004	0.007	1.560	0.050
	16. <i>K. pneumoniae</i> ATCC 10031	0.004	0.007	0.025	0.013
	17. <i>P. mirabilis</i> ATCC 25933	0.025	0.025	0.100	0.050
	18. <i>P. rettgeri</i> ATCC9919	0.007	0.007	0.500	0.025
25	19. <i>S. typhimurium</i> C4045	0.007	0.025	0.100	0.050
	20. <i>S. marcescens</i> C1052	0.025	0.050	0.200	0.200
	21. <i>S. marcescens</i> ATCC 27117	0.007	0.025	0.100	0.100
	22. <i>P. aeruginosa</i> C2027	0.780	1.560	6.250	3.130
30	23. <i>P. aeruginosa</i> ATCC10145	1.560	1.560	12.500	3.130
	24. <i>P. aeruginosa</i> ATCC27853	0.780	3.130	50.000	3.130
	25. <i>P. aeruginosa</i> C4070	1.560	3.130	50.000	6.250

Table 1 (Continued)

Compound		Ex. 9	CTX	CPR	CAZ
5	Strain				
	1. <i>S. pyogenes</i> ATCC 8668	0.007	0.004	0.007	0.100
	2. <i>S. pyogenes</i> C4003	0.007	0.004	0.007	0.200
	3. <i>S. faecalis</i> ATCC 29212	> 100.000	> 100.000	50.000	> 100.000
	4. <i>S. aureus</i> Smith	1.560	1.560	0.390	6.250
10	5. <i>S. aureus</i> ATCC 29213	1.560	1.560	0.780	6.250
	6. <i>S. aureus</i> C4036	3.130	1.560	0.390	6.250
	7. MRSA C2208	> 100.000	> 100.000	> 100.000	> 100.000
	8. <i>S. epidermidis</i> ATCC12228	0.780	0.780	0.200	3.130
	9. <i>E. coli</i> C4002	0.004	0.050	0.050	0.100
15	10. <i>E. coli</i> ATCC 10536	0.007	0.025	0.013	0.050
	11. <i>E. coli</i> ATCC 25922	0.026	0.100	0.050	0.200
	12. <i>E. cloacae</i> C4008	0.013	0.025	0.013	0.050
	13. <i>E. cloacae</i> C4009	0.013	0.100	0.013	0.050
	14. <i>K. oxytoca</i> C4022	1.560	0.780	1.560	0.780
(20)	15. <i>K. pneumoniae</i> C1040	0.004	0.025	0.025	0.050
	16. <i>K. pneumoniae</i> ATCC 10031	0.002	0.002	0.013	0.050
	17. <i>P. mirabilis</i> ATCC 25933	0.025	0.025	0.050	0.050
	18. <i>P. rettgeri</i> ATCC 9919	0.004	0.004	0.013	0.025
25	19. <i>S. typhimurium</i> C4045	0.007	0.050	0.025	0.200
	20. <i>S. marcescens</i> C1052	0.004	0.200	0.050	0.200
	21. <i>S. marcescens</i> ATCC 27117	0.007	0.100	0.050	0.100
	22. <i>P. aeruginosa</i> C2027	0.780	3.130	0.390	0.780
30	23. <i>P. aeruginosa</i> ATCC 10145	1.560	25.000	6.250	1.560
	24. <i>P. aeruginosa</i> ATCC27853	0.780	25.000	3.130	3.130
	25. <i>P. aeruginosa</i> C4070	3.130	50.000	6.250	1.560

- 17 -

Experiment 2: Pharmacokinetics (Plasma Half-Life)

In order to investigate the pharmacokinetics properties of the compounds according to the present invention, the plasma half-life was determined in accordance with the method described in Antimicrobial Agents and Chemotherapy, 26(2), p. 204-207 (1984).

In the experiment, the compound synthesized in Example 5 was selected as the test compound, and CAZ and CPR were used as reference compounds. The results are shown in Table 2 below.

Table 2

Compound	Half-Life ($T_{1/2}$, min)*	Remark
Ceftazidime (CAZ)	12.3	SD Rat
Cefpirome (CPR)	19.5	"
Compound of Example 5	24.0	"

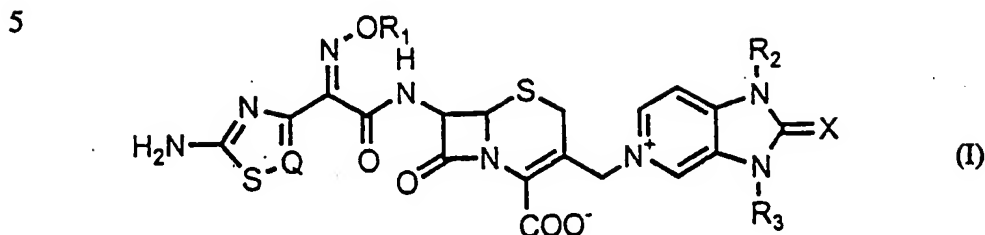
* The half-life shows a mean value.

As can be seen from the foregoing, the compound of the present invention exhibits a significantly longer duration of action than any of the reference compounds.

- 18 -

CLAIMS

1. A cephem compound having the formula:



wherein, Q is a carbon or nitrogen atom; X is an oxygen atom, or a nitroalkyl or cyanoimine group, with the proviso that X cannot be an oxygen atom when Q is a carbon atom; R₁ is a hydrogen atom, or a lower alkyl group, or a lower alkyl group which may be substituted by fluoro, or by a carboxylic group or an inorganic cation salt thereof; and R₂ and R₃ independently are a hydrogen atom or a lower alkyl group; or pharmaceutically acceptable salts thereof.

2. The compound of Claim 1, wherein the compound of formula (I) is one of the following compounds:

()

7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-nitromethylen-yl-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

25 7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-nitromethylenyl-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-cyanoimine-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

30

7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-cyanoimine-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7-β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

35

- 19 -

7- β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[1-methyl-2-(3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

5 7- β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-hydroxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate;

7- β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-carboxymethoxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate; and

10 7- β -[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-fluoromethoxyiminoacetamido]-3-[2-(1H,3H)-oxo-imidazo[4,5-c]pyridiniummethyl]-3-cephem-4-carboxylate.

()

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR 94/00061

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁵: C 07 D 519/00, 501/46; A 61 K 31/545

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁵: C 07 D 519/00, 501/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4 748 172 (A.S.KATNER) 31 May 1988 (31.05.88), claims 1-3; column 2, line 5 to column 3, line 50.	1,2
A	WO, A1, 92/22 556 (CHEIL FOODS & CHEMICALS, INC.), 23 December 1992 (23.12.92), claims 1-3.	1,2

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

18 August 1994 (18.08.94)

Date of mailing of the international search report

06 September 1994 (06.09.94)

Name and mailing address of the ISA/ AT
AUSTRIAN PATENT OFFICE
Kohlmarkt 8-10
A-1014 Vienna
Facsimile No. 1/53424/535

Authorized officer

Mazzucco e.h.

Telephone No. 1/5337058/33

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR 94/00061

The expression "nitroalkyl" in line 12 of claim 1 should be corrected to "nitroalkylenyl" (see corrected abstract) and was read in this sense.

()

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/KR 94/00061

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
US A 4748172	31-05-88	AU A1 34189/84	26-04-85
		AU B2 574107	30-06-88
		CA A1 1225390	11-08-87
		DK A0 4891/84	12-10-84
		DK A 4891/84	18-04-85
		EP A2 138552	24-04-85
		EP A3 138552	19-03-86
		ES A1 536728	16-11-85
		ES A5 536728	16-12-85
		ES A1 8602816	16-03-86
		FI A0 844000	11-10-84
		FI A 844000	18-04-85
		GB A0 8425453	14-11-84
		GB A1 2148289	30-05-85
		GB A0 8627171	10-12-86
		GB A1 2181136	15-04-87
		GB B2 2148289	23-09-87
		GB B2 2181136	25-05-88
		GR A 80670	18-02-85
		HU A2 35687	29-07-85
		HU B 195512	30-05-88
		IL A0 73230	31-01-85
		JF A2 60105685	11-06-85
		NZ A 209833	29-04-88
		PH A 21040	03-07-87
		PT A 79357	01-11-84
		PT B 79357	20-11-86
		SU A3 1360587	15-12-87
		ZA A 8407926	28-05-86
		US A 4692443	08-09-87
WO A1 9222556	23-12-92	AU A1 17861/92	12-01-93
		CA AA 2111459	23-12-92
		CH A 683342	28-02-94
		DE T 4291862	05-05-94
		EP A1 589914	06-04-94
		GB A0 9324280	16-02-94
		GB A1 2271569	20-04-94
		PT A 100590	31-08-93
		SE A 9304027	03-12-93
		SE A0 9304027	03-12-93
		US A 5281589	25-01-94
		ZA A 9203900	24-02-93